

Rejections under 35 U.S.C. § 112, first paragraph

Claims 44-47, 51, 52, 72-75, 79, 100, and 101 stand rejected under 35 U.S.C.

§ 112, first paragraph as containing subject matter that is not described in the specification. In support of this rejection, the Office states (page 2):

Applicant has no support in the originally filed claims or specification for the genus phrase "an intracellular domain that does not signal to said cell to destroy a receptor-bound target cell or receptor-bound target infective agent," present in amended base claims 44 and 79.

- Applicants respectfully disagree.

Turning first to the claims as originally filed, Applicants note that original claim 44 recites "a transmembrane portion derived from a T cell receptor, a B cell receptor, or an Fc receptor which is capable of signalling said cell to destroy a receptor-bound target cell or a receptor-bound target infective agent" (emphasis added). The amendments to present claims 44 and 79 do no more than clarify that it is the transmembrane domain that signals, and that the intracellular domain does not signal the cell to destroy a receptor-bound target cell or receptor-bound target infective agent. This limitation is supported by originally filed claim 44, and, on this basis alone, the rejection should be withdrawn.

Moreover, Applicants have explicitly provided a working example of the presently claimed chimeric immune receptors in the specification. At page 48, lines 20-33, a number of chimeras having intracellular domains of reduced length are described. One such chimera, disclosed at lines 31-33 and in Figure 8A, possesses a transmembrane domain joined to an intracellular domain of only three amino acid residues (amino acids

31-33; RVK). This chimeric receptor is capable of signaling and does so through its transmembrane domain, its intracellular domain merely anchoring the chimera in the cell membrane.

Applicants have previously directed the Office to this working example. In response, however, the Office has dismissed the relevance of this working example, stating (page 3):

Applicant's representative has concluded completely without any direct evidence that the first chimera that has only three amino acids intracellularly, was working as a "nub" to anchor the chimera into the membrane and did not by her assertion act as a signal transmitter.

On this point, the Examiner is directed to additional evidence in the specification demonstrating that the three amino acid intracellular domain of this receptor chimera does not possess signaling activity. In particular, the specification describes several chimeric receptors having larger intracellular domains that include those three amino acids, but which do not possess any significant signaling activity. For example, at page 50, lines 5-10, the specification states:

[T]he Asp<sup>-</sup>, Cys<sup>-</sup> mutated chimera deleted to residue 59 [i.e., having intracellular amino acids 31-33] had no cytolytic activity (Fig. 9B), supporting the hypothesis that association with other chains mediated by the transmembrane Cys and/or Asp residues was responsible for the weak persistence of cytolytic activity in deletions more amino terminal than residue 65.

This chimeric receptor, which possessed an intracellular domain spanning approximately 28 amino acids, and including amino acids 31-33, failed to signal a host cell to destroy a

target. The specification also describes other chimeric receptors having intracellular domains that do not signal target destruction, for example, ones where the tyrosine at position 62 had been converted to a phenylalanine or serine (see, for example, page 51, lines 18-19). Again, these constructs included intracellular amino acids 31-33 and yet did not signal target cell destruction.

Based on these results, one skilled in the art would reasonably conclude that the truncated three amino acid intracellular "nub" present in Applicants' chimeric transmembrane receptor construct similarly does not possess signaling capability. In truth, and as previously asserted, these three intracellular amino acids function merely to anchor the chimeric receptor in the cell membrane, exactly as argued in reply to the previous Office Action. Signaling in this receptor construct is mediated by the transmembrane domain.

In further support of this assertion, Applicants submit herewith a Declaration by Dr. Brian Seed in which Dr. Seed attests to the fact that these three intracellular amino acids do not signal, but rather anchor the chimera in the cell membrane. As stated by Dr. Seed, his data indicate that signaling by this chimeric receptor is mediated by the transmembrane domain, precisely as claimed in instant claims 44 and 79 and their dependent claims.

As a final basis for the present rejection, the Office asserts that Applicants have improperly created a "subgenus" through the present claim amendments. In particular, the

Office states (page 3):

These amendments to the claims represent the creation of a sub-genus from the disclosure of a genus of receptor chimera and the possible disclosure of one chimera which includes a[n] intracellular domain that may or may not signal said cell to destroy a receptor-bound target cell. This is not permitted as is recognized by the case law, "It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads." In re Smith 173 USPQ 679, 683 (CCPA 1972).

First, Applicants disagree with the assertion that the present claims are directed to a subgenus that is not described in the specification. As noted above, Applicants' specification has from its original filing date described and claimed chimeric receptors that signal through their transmembrane domains. Moreover, the present specification provides a working example of a chimeric receptor that signals through a transmembrane (and not an intracellular) domain, precisely as specified by the present amended claims. Consequently, the specification and claims, prior to the present amendments, clearly included these features; no subgenus has been created.

Furthermore, Applicants submit that, to satisfy the written description requirement, one need only communicate to those skilled in the art that the claimed subject matter is intended to be part of their invention. The M.P.E.P. (§ 2163.02; Eighth Edition, August 2001) states:

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she has invented what is claimed."

To satisfy this standard, the Federal Circuit has held that the specification need only convey with reasonable clarity to a skilled artisan that the inventor "was in possession of the invention" at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991).

Applicants' specification plainly meets this standard by providing a working example of a chimeric receptor that signals through a transmembrane, rather than an intracellular, domain. Moreover, Applicants have, from the time they filed this application, claimed this type of receptor as part of their invention. One skilled in the art would therefore certainly recognize that, at the time of filing, the inventors were in possession of chimeric receptors that signaled through transmembrane (rather than intracellular) domains. The written description requirement of § 112, first paragraph has been satisfied by Applicants, and the rejection of claims 44-47, 51, 52, 72-75, 79, 100, and 101 under § 112, first paragraph, should be withdrawn.

#### Status of Pending Claims 66 and 68

With regard to the pending claims, Applicants note, in reference to the restriction requirement mailed on September 1, 1999 and Applicants' reply mailed on September 30, 1999, that claims 66 and 68 are part of elected Group I and do not read on the elected species. However, no mention of claims 66 and 68 was made in the Summary of the first Office Action on the merits mailed on November 16, 1999 or in any Office Action

thereafter. As these claims have not been canceled, Applicants submit that the current status of claims 66 and 68 is pending, but withdrawn from consideration.

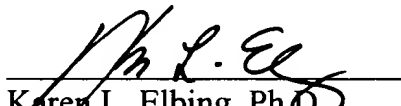
### CONCLUSION

Applicants submit that the claims are now in condition for allowance, and such action is hereby respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including April 23, 2002. If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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